Mathematical modelling of lymphopenia induced proliferation*

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Objectives

Biological background See poster "A combined mathematical modelling and experimental investigation of naïve T-lymphocyte homeostasis ", Thea Hogan et al.

- To estimate parameters of mathematical models (Smith-Martin and Gett-Hodgkin) for fitting the CFSE data
- To compare mathematical models
- Data: F5 and OT-1 cells transferred into lymphopenic Rag1$^{-/-}$ transgenic mice (2-3 mice per sampling time, 5-9 sampling times per experiment, 2 experiments by type of cells).

Mathematical models

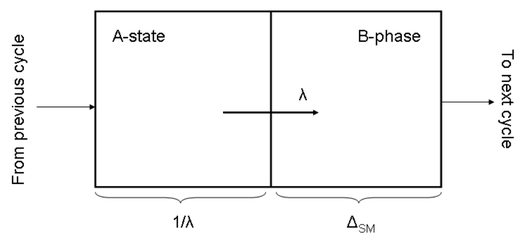
Smith-Martin approach [1] assumes that each cell cycle (i) separated in two parts: A-state, which approximately corresponds to G_1 phase, with stochastic duration and B-phase, which duration corresponds to the rest phases of the cell cycle, with fixed duration Δ_{SM}.

$$\dot{A}_i(t) = 2\lambda \cdot e^{-\delta_B \cdot \Delta_{SM}} \cdot A_{i-1}(t-\Delta_{SM}) - (\lambda+\delta_A)A_i(t) \qquad \{A_0(t=T) = N_0\}$$

$$B_i(t) = \int_0^{\Delta_{SM}} \lambda A_i(t-s)e^{-\delta_B \cdot s}$$

$$p_i(t) = \frac{2^{-i}(A_i(t)+B_i(t))}{\sum_i 2^{-i}(A_i(t)+B_i(t))}$$

We used 3 types of dependence of λ: $\lambda = const$, $\lambda = \lambda_0 \cdot e^{-\mu \cdot t}$, $\lambda = \lambda_0 \cdot e^{-\mu \cdot i}$.
$\delta_A = \delta_B = \delta_0 \cdot \ln(1+\delta \cdot i)$, $\{\delta_0 = 1\}$.



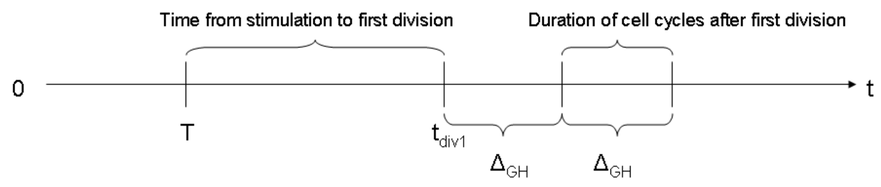
Parameters:
λ – rate of transfer from A-state to B-phase.
Δ_{SM} – duration of B-phase.
T – time, when cells are triggered to division.
μ – progressive reduction in division rate.

Gett-Hodgkin approach [2] assumes that the first division after stimulation for division (in time T) occures in time t_{div1} with duration and distributed according to some given law $\phi(\alpha, \beta; s)$ (we used Weibul, Gamma and Log-Normal for comparison). All remain divisions (i) occurs within the fixed time Δ_{GH}.

$$p_{i=0}(t) = 1 - \int_0^{t-T} \phi(\alpha, \beta; s)ds$$

$$p_{i>0}(t) = \int_{t-T-i\Delta_{GH}}^{t-T-(i-1)\Delta_{GH}} \phi(\alpha, \beta; s)ds$$

α and β are scale and shape parameters respectively.



Parameters:
α, β – scale and shape parameters of distribution of time to first division.
Δ_{GH} – duration of all division after the first.
T – time, when cells are triggered to division.

Methods of parameters estimation $\left(\vec{\theta} = \lambda_0, \Delta_{SM}, T, \mu\right)$ or $\left(\vec{\theta} = \alpha, \beta, \Delta_{GH}, T\right)$

Minimization of *weighted sums of squared residuals*:

$$WSSR = \sum_{i,j,k} \frac{(p_i(t_k;\vec{\theta}) - f_{ij}(t_k))^2}{SD_{ij}(t_k)^2}$$

$p_i(t_k;\vec{\theta})$ – frequencies of precursors with parameters vector $\vec{\theta}$, calculated from the model, $f_{ij}(t_k)$ – observed frequencies. Summation over all divisions (i), mice (j) and sampling times (t_k). A standard deviation SD over all mice in a given sampling time and given number of divisions was used for measurement error function. For calculation of CIs bootsraping was used.

Results

Parameters of both models (Smith-Martin and Gett-Hodgkin) were estimated using the experimental data, obtained by Hogan et al. (see poster "A combined mathematical modelling and experimental investigation of naïve T-lymphocyte homeostasis ").

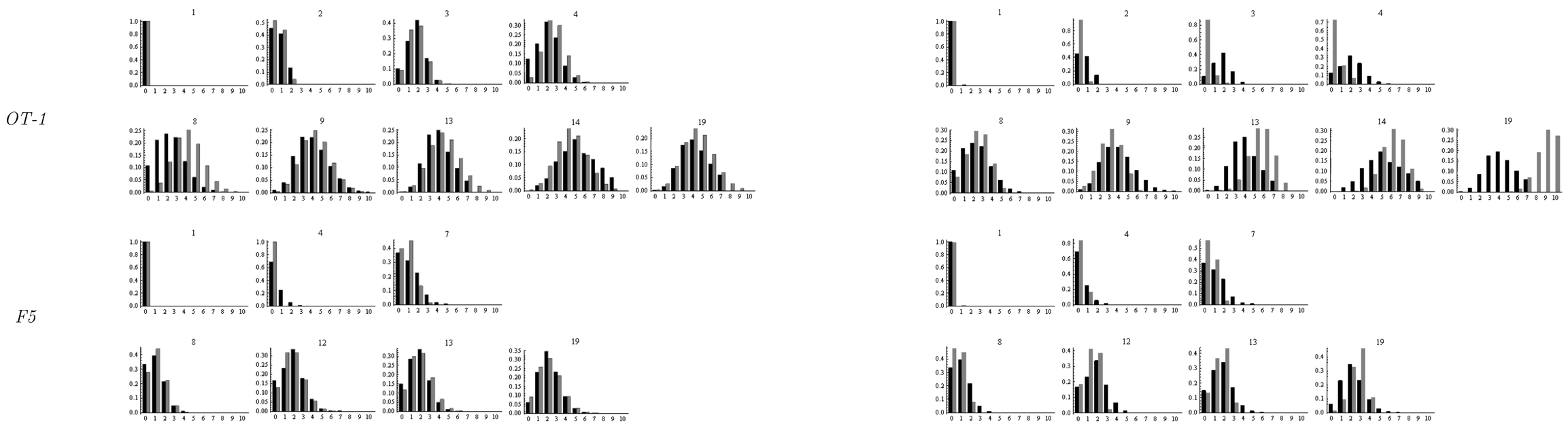
The best fit was obtained: for Smith-Martin model for the case $\lambda = \lambda_0 e^{-\mu \cdot t}$ with cell death; for Gett-Hodgkin model for the Weibull distribution.

Smith-Martin model

Receptor	λ_0 $[day^{-1}]$	Δ $[day]$	T $[day]$	δ	μ $[day^{-1}]$	AIC
OT-1	4.428	0.287	1.402	0	0.425	241
F5	1.895	0.529	4.610	0.006	0.240	109

Gett-Hodgkin model

Receptor	Δ $[day]$	T $[day]$	T_{d1} $[day](\alpha)$	SD_{d1} $[day](\beta)$	AIC
OT-1	1.582	0.078	5.121 (2.922)	1.906 (5.741)	771
F5	5.263	0.035	8.177 (2.040)	4.199 (9.230)	621



Notes: 1. Numbers on the top of each plot – sampling days. 2. X-axes – number of divisions, Y-axes – frequencies. Black bars – observed frequencies, gray bars – frequencies from the model.

1. Smith-Martin model fits experimental data better than Gett-Hodgkin for both types of cells (lower AIC).
2. Cells with OT-1 receptors divides more intensively than with F5 (higher λ and lower T for OT-1).

Ongoing work

Methods of parameters estimation

Likelihood approach:

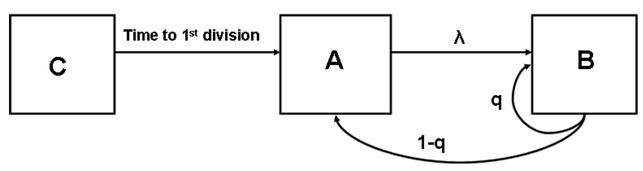
- allow to compute CIs immediately (using Information matrix)
- model for measurement error is tricky

Extension of mathematical model

The cell is allowed to do several cycle staying in B-state:

$$\frac{d}{dt}A_i(t) = 2(1-q)B_{i-1}(t, \tau = \Delta) - \lambda A_i(t)$$

$$\frac{\partial B_i(t,\tau)}{\partial t} + \frac{\partial B_i(t,\tau)}{\partial \tau} = -\delta_B(\tau) \qquad \{B_i(t, \tau = 0) = qB_{i-1}(t, \tau = \Delta) + \lambda A_i(t)\}$$



References
1. Smith, J. & Martin, L. (1963) Do cells cycle? *PNAS*, **70**, 1263-1267.
2. Gett, A. & Hodgkin, P. (2000) A cellular calculus for signal integration by T cells. *Nature Immunology*, **1**, 239-244.